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Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews (Protocol)

Craig SS, Dalziel SR, Powell CVE, Graudins A, Babl FE, Lunny C

Craig SS, Dalziel SR, Powell CVE, Graudins A, Babl FE, Lunny C.
Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews.
Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD012977.
DOI: 10.1002/14651858.CD012977.

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[Overview of Reviews Protocol]

Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews

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Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 3, 2018.

Citation: Craig SS, Dalziel SR, Powell CVE, Graudins A, Babl FE, Lunny C. Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD012977. DOI: 10.1002/14651858.CD012977.

ABSTRACT

This is a protocol for a Cochrane Review (Overview). The objectives are as follows:

Main objectives

- To summarise Cochrane Reviews on the efficacy and safety of interventions for escalation of treatment for children with acute exacerbations of asthma

Secondary objectives

- To identify gaps in the current evidence base that will inform recommendations for future research and subsequent Cochrane Reviews
- To categorise information on reported outcome measures used in trials of escalation of treatment for acute exacerbations of asthma in children, and to make recommendations for development and reporting of standard outcomes in future trials and reviews
- To identify relevant research papers that have been published since the date of publication of each included review

BACKGROUND

Description of the condition

Asthma is defined as "a chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyper-responsiveness" (Papadopoulos 2012). Clinical features include recurrent episodes of cough, shortness of breath, wheeze, or chest tightness (Papadopoulos 2012), which may be triggered by viral respiratory infection, exercise, a change in the weather, or exposure to allergens or irritants (GINA 2017).

Airflow obstruction results primarily from episodic bronchoconstriction due to contraction of airway smooth muscle. However, other mechanisms also contribute, including mucosal oedema, inflammation, mucus hyper-secretion, airway hyper-responsiveness, and airway remodelling (NHLBI 2007).

The diagnosis and management of asthma are complicated in younger children, particularly those from birth to five years (Cave 2014). In this age group, viral-induced wheezing is very common and has clinical features overlapping those of asthma but does not necessarily have the same longer-term implications (Martinez 1995; Caudri 2009; Konstantinou 2013).

Care of a child with asthma requires long-term management aimed at preventing recurrent exacerbations, as well as acute management of symptomatic exacerbations. Treatment for asthma addresses the underlying pathophysiological mechanisms of inflammation and bronchoconstriction.

An asthma exacerbation is defined as an "acute or subacute episode of progressively worsening shortness of breath, cough, wheezing, and chest tightness - or some combination of these symptoms" (NHLBI 2007). First-line therapy for management of acute exacerbations of asthma is well established and requires titrated oxygen delivery and administration of intermittent inhaled short-acting beta$_2$-agonists (SABAs) and oral corticosteroids (OCSs) (NHLBI 2007; National Asthma Council Australia 2016; GINA 2017).

Description of the interventions

Most children with asthma have mild or moderate exacerbations and respond well to first-line therapy (Powell 2003; Kelly 2004; Giordano 2012; O'Connor 2014). A minority of children with severe exacerbations are unresponsive to first-line therapy and require escalation of treatment (O'Connor 2014; Biagini Myers 2015; Morris 2015). Many options are available for escalation of treatment, but the choice of regimens shows considerable variability amongst clinicians (Babl 2008; Lyttle 2015).

Escalation of treatment can be grouped into the following broad categories.

- Additional inhaled bronchodilators, including continuous inhaled β_2-agonists, anticholinergic medications such as ipratropium, and nebulised magnesium sulfate.
- Parenteral bronchodilators, including selective β_2-agonists such as salbutamol or terbutaline; adrenaline (epinephrine), an agonist at both α- and β-receptors; magnesium sulfate; methylxanthines such as theophylline or aminophylline; and ketamine. Subcutaneous, intramuscular, and intravenous routes may be utilised, and intravenous treatment may be delivered as a single loading dose or as a continuous infusion.
- Interventions to reduce the work of breathing, including inhalation of heliox (a mixture of helium and oxygen), administration of high-flow humidified nasal oxygen therapy, or provision of non-invasive ventilation with the use of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP).

How the intervention might work

Bronchodilators

Relief of bronchoconstriction, a major therapeutic target in an acute exacerbation of asthma, is achieved by several pharmacological agents acting by various mechanisms. Inhaled short-acting β_2-agonists (SABAs), such as salbutamol and terbutaline, are effective, provide a rapid onset of action, and are accepted as first-line therapy for acute asthma exacerbations (Vezina 2014). In young children, administration using a spacer or holding chamber is preferred over delivery via nebuliser (Ferguson 2006). In patients with severe exacerbations unresponsive to first-line administration of intermittent inhaled SABA, clinicians may wish to administer continuous inhaled SABA to saturate all available respiratory tract β_2-receptors and achieve maximum bronchodilation from this pathway (Kenyon 2014).

Inhaled anticholinergic agents such as ipratropium bromide are thought to cause bronchodilation by relieving cholinergic bronchoconstriction and reducing mucosal oedema and airway secretions (Vezina 2014). Although not as effective as β_2-agonists, it has been suggested that combining both medications may lead to greater bronchodilation than use of either agent alone (Griffiths 2013).

Magnesium sulfate has been demonstrated to be an effective bronchodilator and may be administered by nebuliser or by the intravenous route. Its mode of action is thought to relate to direct smooth muscle relaxation; however, additional mechanisms may relate to blocking calcium ion influx into smooth muscle cells, modulating mast cell histamine release, anti-inflammatory properties, and cholinergic neural transmission (Powell 2012). Some evidence suggests that simultaneous administration of magnesium sulfate and a β_2-agonist has an additive bronchodilator effect, perhaps owing to magnesium sulfate augmenting the β-receptor agonist response (Neame 2015).

In the setting of severe acute asthma, it has been suggested that inhaled β_2-agonists may not reach their site of action through the

airway owing to significant airflow obstruction, and that systemic (subcutaneous or intravenous) administration of bronchodilators may lead to a more rapid therapeutic response (Travers 2012).

Adrenaline (epinephrine) is a potent β-agonist with bronchodilating effects similar to the more selective β_2-agonists. Historically, parenteral adrenaline was a standard therapy for acute asthma (Rees 1967; Shim 1984); however, similar clinical efficacy and the less invasive nature of inhaled bronchodilators as reported by Naspitz 1987 have led clinicians to reserve this treatment as an option for severely ill patients unresponsive to inhaled therapy (Hon 2017).

Methylxanthines such as theophylline and aminophylline have been used for many years to treat patients with asthma. Bronchodilator effects may be due to inhibition of phosphodiesterase, leading to accumulation of cyclic adenosine monophosphate (cAMP) in smooth muscle cells, adenosine antagonism, and release of catecholamines (Neame 2015). Other actions are thought to include anti-inflammatory and immunomodulatory effects (Neame 2015).

Ketamine is commonly used in the emergency department (ED) for procedural sedation, analgesia, and intubation, and has many effects, including dissociative anaesthesia, analgesia, amnesia, and anxiolysis. It can also induce bronchodilation, possibly as a sympathomimetic effect or a direct effect on bronchial smooth muscle (Jat 2012). Other potential effects include immunomodulation and inhibition of vagal outflow (Goyal 2013).

Interventions to reduce the work of breathing

Room air comprises nitrogen (79%) and oxygen (21%). Heliox (helium-oxygen mixture) is produced when helium replaces nitrogen, leading to a less dense gas mixture. Theoretically, this may reduce turbulent airflow and airflow obstruction in patients with asthma. Heliox has also been used to deliver nebulised therapy, as it has been suggested that it may lead to improved transport of medication to the distal airways (Rehder 2017).

Non-invasive respiratory support can be delivered with the use of high-flow nasal cannulae (HFNC), continuous positive airway pressure (CPAP), or bi-level positive airway pressure (BiPAP). Patients with severe asthma often develop elevated intrinsic positive end-expiratory pressure (PEEP). It is theorised that delivery of extrinsic positive pressure via face mask or nasal cannulae may overcome this intrinsic pressure, thereby reducing the work of breathing.

High-flow nasal cannulae provide warmed, humidified gas delivered via nasal prongs at a flow rate that exceeds the patient's peak inspiratory flow rate. This results in washout of anatomic dead space and also provides some PEEP, although the PEEP delivered is less consistent than that provided by CPAP or BiPAP (Rehder 2017). High-flow delivery is more comfortable and therefore is better tolerated with less requirement for sedation than other methods of non-invasive respiratory support (Baudin 2017).

CPAP provides constant pressure throughout the respiratory cycle, and BiPAP provides variable pressure according to phases of the respiratory cycle, with higher pressure delivered during inspiration. Positive effects of CPAP and BiPAP include a direct bronchodilating effect, improved alveolar recruitment, improved airflow, re-expansion of areas of collapse, reduced hyperinflation, and reduced work of breathing (Korang 2016).

Why it is important to do this overview

Clinical rationale

Asthma is a common reason for paediatric visits to the ED (Alpern 2006; Acworth 2009); it is one of the most common reasons for a child to be admitted to hospital after an ED visit (Weiss 2011). In the USA, the rate of paediatric ED visits for asthma increased by 13.3% between 2001 and 2010 (Nath 2015), and in the UK, it is estimated that a child is admitted to hospital every 20 minutes owing to an asthma attack (Asthma UK).

The care of children with asthma is based upon escalation of treatment in response to disease severity: Mild disease receives less intensive treatment than severe disease. Broadly speaking, interventions take the form of inhaled bronchodilators, parenteral (intravenous or subcutaneous) pharmacotherapy, and mechanical efforts to reduce the work of breathing. With increasing 'level of treatment' come risks of increasing costs, patient discomfort, potential for complications, and requirement for monitoring and/or transfer to intensive care units. Some treatments - particularly intravenous bronchodilators or assisted ventilation - are given in higher-acuity settings such as intensive care, and other treatments may be given in a standard ward environment.

Variation in the management of acute severe asthma in children is considerable and may be due to considerations around efficacy and safety, cost, clinical experience, and individual practitioner preference. A recent survey of emergency physicians in the UK and Ireland found that over half preferred salbutamol as first-line intravenous treatment, while 28% preferred magnesium sulfate and 15% preferred aminophylline (Lyttle 2015). An earlier survey of paediatric emergency specialists in Australia and New Zealand found that aminophylline was used by 45%, intravenous magnesium sulfate by 55%, and intravenous salbutamol by 87% of respondents (Babl 2008). A recent prospective study of 24 EDs in the UK and Ireland found wide variation in the prevalence of intravenous treatment for acute paediatric asthma, ranging from 0% to 19.4% (Morris 2015).

With a large number of treatment options and wide variation in self-reported and actual practice, it is important to have a single comprehensive and user-friendly document that provides the best available evidence upon which to base clinical decisions. There is a need to present available evidence clearly to assist clinicians and other users. The purpose of a Cochrane overview is to systemati-

cally summarise evidence from a range of Cochrane intervention reviews for a single health condition (Becker 2011). The overview will document current evidence for the efficacy of various available interventions and will provide information about toxicity and adverse effects.

Potential additional benefits of this overview will include a clear foundation upon which further research can be based and an understanding of reported outcome measures, which may be used to assist in development of a set of core outcome measures for future clinical trials.

Methodological rationale

Currently, the Cochrane Airways Group has prepared approximately 50 published reviews on the effectiveness of various interventions for acute asthma. This includes 43 reviews on pharmacotherapy and another seven reviews on non-pharmacotherapy interventions. Given the large number of potentially relevant reviews and the likely heterogeneity in eligibility criteria and study outcomes, we have chosen to utilise an overview design rather than a network meta-analysis as the first step in assessing the literature.

OBJECTIVES

Main objectives

- To summarise Cochrane Reviews on the efficacy and safety of interventions for escalation of treatment for children with acute exacerbations of asthma

Secondary objectives

- To identify gaps in the current evidence base that will inform recommendations for future research and subsequent Cochrane Reviews
- To categorise information on reported outcome measures used in trials of escalation of treatment for acute exacerbations of asthma in children, and to make recommendations for development and reporting of standard outcomes in future trials and reviews
- To identify relevant research papers that have been published since the date of publication of each included review

METHODS

Criteria for considering reviews for inclusion

Types of reviews

We will include reviews on treatment of patients with acute asthma published in the *Cochrane Database of Systematic Reviews* (CDSR). We will include Cochrane Reviews of randomised controlled trials (RCTs) and quasi-randomised controlled clinical trials (CCTs).

Types of participants

We will include reviews of children with a physician-diagnosed acute exacerbation of asthma. We will define a child as any person aged younger than 18 years. However, as the definition of 'child' may vary between reviews, we intend to include any studies in which a population is described as children, and we will record the ages included within each review. We will include reviews of adults and children in which the results for children can be separated from the results for adults.

Types of interventions/comparisons

We will include all treatments that may be considered escalation of therapy for acute exacerbations of asthma. We will not include reviews examining interventions including only corticosteroids or intermittent inhaled β_2-agonists.

We will divide treatments into the following categories, consistent with steps in the escalation of therapy (inhaled treatment, parenteral treatment, and other interventions to reduce the work of breathing).

- Inhaled bronchodilators.
- ○ Continuous inhaled β_2-agonists (via spacer or nebuliser).
- ○ Anticholinergic medications.
- ○ Magnesium sulfate.
- Parenteral bronchodilators.
  - ○ β_2-agonists.
  - ○ Adrenaline/epinephrine.
  - ○ Magnesium sulfate.
  - ○ Methylxanthines.
  - ○ Ketamine.
- Interventions to reduce the work of breathing.
  - ○ Heliox.
  - ○ High-flow nasal cannulae.
  - ○ Non-invasive ventilation (CPAP or BiPAP).

Types of comparisons

We will include reviews with all possible comparisons, that is, versus placebo and/or versus another active comparator (ongoing first-line treatment or an alternative intervention).

Types of outcome measures

Primary outcomes

- Length of stay (duration of ED stay and duration of inpatient stay)
- ED disposition (hospital admission/intensive care unit (ICU) admission/ED discharge)
- Number of adverse events in each treatment group

Secondary outcomes

- Symptom scores/clinical asthma scores (such as the Pulmonary Index (Becker 1984), the Clinical Asthma Score (Parkin 1996), the Pediatric Respiratory Assessment Measure (Ducharme 2008), and any other scores identified in the included reviews)
- Lung function (peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV_1), and other measures identified in included reviews)
- Adverse events (vomiting, nausea, tremor, tachycardia, convulsions, and any other adverse events identified in included reviews)
- Vital signs (pulse, blood pressure, respiratory rate, and pulse oximetry)
- Requirement for additional bronchodilator treatment
- Requirement for respiratory support (intubation, non-invasive ventilation)
- Economic outcomes such as healthcare costs

We will report on the primary and secondary outcomes outlined above. However, we will tabulate all outcomes identified in the overview to present a taxonomy of outcomes for future reviews on this topic.

Search methods for identification of reviews

We will search for systematic reviews in the Cochrane Library using the filter for reviews. We will identify Cochrane Review protocols and titles for future inclusion. We will use the search terms "asthma" and "respiratory sounds" (which includes the medical subject heading (MeSH) term for "wheeze"). Our search strategy is detailed in Appendix 1.

We will include only the most recently published version of each review. We will not include protocols and earlier versions of a review that have been superseded. We do not intend to include systematic reviews from outside the Cochrane Library. If multiple reviews address the same question, we will examine them for unique content, and if none is found, we will include the most up-to-date review. If multiple reviews address the same question and unique content is found in each, we will include them and will extract the unique data.

To identify relevant research papers that have been published since the data of publication for each included review, we intend to utilise the search strategy of each included review. We will supplement this by cross-checking against current British Thoracic Soceity/Scottish Intercollegiate Guidelines Network (BTS/SIGN) and Global Initiative for Asthma (GINA) guidelines.

Data collection and analysis

Selection of reviews

We will assess in two stages the eligibility of identified Cochrane Reviews. Two independent review authors will screen each title and abstract. A third review author will resolve discrepancies when the two review authors cannot reach consensus. Two independent review authors will assess in full text all titles/abstracts that were selected by consensus. Again, we will attempt to resolve discrepancies in consensus between the two review authors by including a third review author if required.

We will attach a table of excluded reviews as an appendix.

Data extraction and management

Two review authors will independently extract data using an electronic data extraction form specifically designed for this project. We will involve a third review author to resolve disagreements. Data to be extracted (see Appendix 2) include the following.

- Details of the review, including first author name, year of publication, number of included primary studies (countries and years in which the original studies were conducted), eligibility criteria of included reviews, numbers of included participants, and sample size of included RCTs. We will map systematic reviews to their included RCTs.
- Details of trial populations, including age and severity of asthma (including inclusion criteria and definition of exacerbation of asthma for each review, treatment before enrolment, and severity of asthma at enrolment).
- Settings (ED, hospital ward, ICU).
- Types of interventions.
- Dose, duration, and frequency of intervention administration.
- Description of the comparison (placebo, regular doses of bronchodilators).
- Description of outcome measures used, including our predefined primary and secondary outcomes and all other outcomes reported.
- Timing of determination of outcome measures and duration of follow-up.
- Risk of bias assessments of RCTs included in the reviews.
- For each predetermined primary and secondary outcome measure, and for all additional outcomes, numbers of participants in intervention and control groups; control event rate; effect estimates for the pooled risk ratio; odds ratio, hazard ratio, standardised mean difference, or absolute risk reduction and corresponding 95% confidence intervals (if not provided, we

will calculate these, using the equations published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schüneman 2017)); details of statistical tests for heterogeneity, including the Chi^2 test and the I^2 test.

- Conclusions of each review.
- Review recommendations for further research.
- Quality assessment tools used (e.g. GRADE), along with the mean or median and the range of any reported quality scores.

If the included systematic review includes all studies relevant to a particular outcome, we will extract summary data alone. We will extract only data from studies conducted exclusively among children or for which authors of the systematic review have been able to enter data from children.

If we identify overlapping information across systematic reviews at the data extraction stage, we will extract data only from the most recently published review. We will acknowledge overlap among different reviews (overlapping trials), depict any potential overlap in tables, and discuss this limitation in the results.

If we identify discrepant data across systematic reviews, we will extract data from all included reviews and will reconcile the discrepancies by contacting the authors of included reviews, retrieving primary studies from the included reviews, and searching relevant trial registries. We will discuss potential discrepancies in data in the Results section.

We will present the data in a series of summary tables.

Assessment of methodological quality of included reviews

Two review authors will independently assess the risk of bias of included reviews using the Risk of Bias in Systematic Reviews (ROBIS) tool (Whiting 2016). The ROBIS tool (see Appendix 3) consists of three phases: assessment of relevance of the systematic review to the study question, identification of potential concerns regarding the review process, and a judgement of risk of bias. We will report in a table assessment for individual ROBIS items or domains (along with the rationale for judgements for each assessment).

We define a high-quality meta-analysis as one that has a low risk of bias judgements for the first three domains of the ROBIS tool, namely, specification of study eligibility (domain 1), methods used to identify and/or select studies (domain 2), and methods used to collect data and appraise studies (domain 3) (Whiting 2016). We will choose the meta-analysis that we judged as having low risk of bias in all four ROBIS domains, as well as the meta-analysis that most closely matches our overview PICO criteria if we find more than one high-quality meta-analysis.

We will use the risk of bias assessment to conduct sensitivity analyses, but we will not exclude reviews on the basis of the risk of bias assessment.

We will present a summary of this information according to guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

Quality of evidence in included reviews

Two overview authors will independently evaluate the certainty of evidence on the basis of judgements made by the authors of the original Cochrane Reviews, if provided.

We will assess the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Balshem 2011).

First, we will extract the GRADE assessments for each systematic review for each independent outcome. We will first assess whether the domain judgements are consistent; if they are inconsistent, we will try to reconcile the inconsistency by comparing extracted data between the reviews for missing or discrepant data, contacting the authors of the primary studies, or searching trial registries, if two or more systematic reviews report GRADE assessments for the same outcome. We will choose the highest-quality meta-analysis from which to extract effect estimates for our GRADE assessment of inconsistency and imprecision if we continue to note inconsistency in the reported GRADE domains (or none reported).

We will independently conduct this assessment by constructing 'Summary of findings' tables using GRADEpro software (GradePro 2015)if the original review published no GRADE assessment, of if outcome data in our overview have been re-analysed from a subset of primary studies within a review.

We will base our assessment of the certainty of evidence in included reviews on data provided in the 'Characteristics of included studies', 'Risk of bias', and 'Summary of findings' tables provided in the included reviews, and we will present a summary of this information according to guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

We will summarise the evidence for our primary outcomes in a 'Summary of findings' table.

Dealing with missing data

We will address data missing from an included systematic review or variation in information reported across reviews by retrieving and examining the full reports of RCTs included in the systematic reviews; contacting systematic review authors for missing information or clarification; searching systematic review protocols; and/or searching registries of systematic reviews or clinical trials for further information. This overview will include discussion on potential discrepancies with information provided in the original reviews.

Data synthesis

We will tabulate PICO (population, intervention, control, and outcome) elements at the review level. Results tables will include effect estimates, 95% confidence intervals (CIs), and measures of heterogeneity/risk of bias, as appropriate.

We aim to group data into the three broad groups described above: inhaled bronchodilators, parenteral bronchodilators, and interventions to reduce the work of breathing. We intend to compare all outcomes between inhaled bronchodilators (e.g. standard therapy/placebo vs continuous nebulised SABA vs inhaled magnesium), between parenteral bronchodilators (e.g. standard therapy/placebo vs aminophylline vs magnesium vs ketamine vs salbutamol vs terbutaline), and between interventions to reduce the work of breathing (standard therapy/placebo vs CPAP vs BiPap vs heliox vs HFNC). We will extract effect estimates from the included systematic reviews, categorised by intervention and primary and secondary outcomes, and will present them in tables and figures.

We will structure narrative descriptions of effect estimates of the included reviews according to systematic review risk of bias and GRADE assessment.

We will also assess the impact of inclusion criteria (severity of asthma), treatment before enrolment (including type of first-line intervention applied), and control treatment on the effects of interventions.

The choice of effect estimate for summary and tabulation will depend on the outcomes reported in various reviews. We intend to standardise the outcomes reported if an outcome is expressed differently between reviews. We will standardise to risk ratios (RRs) or odds ratios (ORs) for dichotomous outcomes. We will standardise to mean differences (MDs) or standardised mean differences (SMDs) by using equations published in the *Cochrane Handbook for Systematic Reviews of Interventions* for continuous outcomes (Higgins 2011a).

The exact method chosen for graphical display will depend on the number of studies available for each particular outcome. We will use Review Manager 5 (Cochrane 2014) to generate forest plots of standardised effect measures and will use these to graphically present the results, with each review representing one line in the forest plot. Other options include using harvest plots as described in Crick 2015 or bar graphs.

We will discuss the limitations of currently available evidence with regards to heterogeneity of inclusion criteria for each review, consistency of effect size for each intervention, and consistent use of outcome measures. We will identify gaps in the current evidence base and will make recommendations for future research.

Assessment of non-statistical heterogeneity

We will determine whether there is clinical heterogeneity between reviews (i.e. differences in severity of asthma or differences in treatment administered before enrolment) by assessing the inclusion criteria of each systematic review. We will also assess clinical heterogeneity within each systematic review that will contribute to the quality assessment of each review.

We will examine the heterogeneity of evidence for each primary outcome by summarising the range of I^2 variation. Heterogeneity is considered not important if the I^2 variation is 0 to 40%, moderate if 30% to 60%, substantial if 50% to 90%, and considerable if 75% to 100% (Deeks 2017).

We will identify commonly used outcomes and will categorise them in a taxonomy by creating a list of all outcomes and discussing their categorisation among the review author group until consensus is reached. This taxonomy will inform recommendations for a core set of outcome measures, which may be applicable in future RCTs.

Subgroup analysis

Given the pathophysiological differences between preschoolers and older children, we intend to subgroup studies of children from birth to five years of age and children aged six to 18 years (or younger and older children as defined by review authors) and to provide separate summary tables within the overview.

Finally, we will group studies occurring in the ED/outpatient setting separately from those occurring in the inpatient setting (ward or intensive care unit).

We will extract summary event data for each treatment/placebo group from the included reviews for all subgroup analyses.

Sensitivity analysis

We will conduct sensitivity analysis based on the ROBIS assessment of systematic reviews by comparing results of all reviews against data derived only from reviews in which the ROBIS tool identified no domains with a "high" level of concern (i.e. by excluding studies that have one or more domains in the ROBIS tool rated as causing a "high" level of concern).

ACKNOWLEDGEMENTS

We thank Liz Stovold, Information Specialist, Cochrane Airways Group, for advice on search strategies for this overview.

Katherine Pike was the Editor for this review and commented critically on the review.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Airways Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy for *Cochrane Database of Systematic Reviews*

#1 MeSH descriptor: [Asthma] explode all trees
#2 MeSH descriptor: [Respiratory Sounds] this term only
#3 asthma*:ti,ab,kw
#4 #1 or #2 or #3

Appendix 2. Data collection tool

Details of the review

- First author name
- Year of publication
- Number of included primary studies
- Countries and years pf the original studies
- Eligibility criteria of included studies
- Numbers of included participants
- Sample size of included RCTs
- Details of included RCTs

Participant characteristics

- Age
- Severity of asthma
- Definition of exacerbation of asthma for each RCT
- Treatment before enrolment

Setting

- Emergency department
- Hospital ward
- Intensive care unit

Types of interventions

- Name of medication/intervention
- Dose of medication/intervention
- Duration of treatment
- Frequency of intervention administration

Description of the comparative treatment (placebo, regular doses of bronchodilators)

Description of outcome measures used

For each outcome measure

- Number of participants in the intervention group
- Number of participants in the control group
- Intervention event rate
- Control event rate
- Effect estimates for pooled results (risk ratio, odds ratio, hazard ratio, standardised mean difference, or absolute risk reduction and corresponding 95% confidence intervals)
- Details of statistical tests for heterogeneity
    - Chi^2 test
    - I^2 test

Predefined primary outcome measures

- Length of stay

    - Emergency department length of stay
    - Hospital length of stay
- Emergency department disposition
    - Hospital admission
    - ICU admission
    - ED discharge
- Adverse events
    - Vomiting
    - Nausea
    - Tremor
    - Tachycardia
    - Arrhythmia
    - Convulsion
    - Other (specify)

Predefined secondary outcome measures

- Symptom scores/clinical asthma scores
    - Name of score
    - Definition/reference
    - Time of recording of outcome measure
    - Interpretation of score result (cutoff)
- Lung function tests
    - Examples: peak expiratory flow rate, forced expiratory volume in one second, and other measures
    - Name of test
    - Definition/reference
    - Time of recording of outcome measure
    - Interpretation of test result (cutoff)
- Vital signs
    - Examples: pulse, blood pressure, respiratory rate, pulse oximetry
    - Name of vital sign
    - Definition/reference
    - Time of recording of vital signs
    - Interpretation of vital signs results (cutoff)
- Requirement for additional bronchodilator treatment
    - Name of outcome measure
    - Definition/reference
    - Time of recording of outcome
    - Interpretation
- Requirement for respiratory support
    - Intubation
    - Time of recording of outcome
- Non-invasive ventilation
    - Name of outcome measure (CPAP, BiPap, etc.)
    - Definition/reference
    - Time of recording of outcome
    - Interpretation
- Economic outcomes/healthcare costs
    - Definition/reference
    - Time of recording of outcome
    - Interpretation
- Additional outcome measures
    - Name of outcome measure
    - Definition/reference

- Time of recording of outcome
- Interpretation

Risk of bias assessments of RCTs included in the reviews.
Quality assessment tools used (e.g. GRADE) along with the mean or median and range of any reported quality scores.
Conclusions of each review.
Review recommendations for further research.
If the included systematic review includes all studies relevant to a particular outcome, we will extract summary data alone. If data are required to be extracted from a subgroup of studies (i.e. only children), then we will extract study-level data from all RCTs included in the review. These data will include numerical primary study results and risk of bias data.

Appendix 3. ROBIS tool

The ROBIS tool to assess risk of bias in systematic reviews consists of the following assessment criteria.

Phase 1. Assessing relevance (optional)

For intervention reviews, assessment of patients/populations; interventions; comparators; and outcomes.

Phase 2. Identifying concerns with the review process

Domain 1. Study eligibility criteria.
- Did the review adhere to predefined objectives and eligibility criteria?
- Were the eligibility criteria appropriate for the review question?
- Were eligibility criteria unambiguous?
- Were all restrictions in eligibility criteria based on study characteristics appropriate?
- Were any restrictions in eligibility criteria based on sources of information appropriate?

Domain 2. Identification and selection of studies
- Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?
- Were methods additional to database searching used to identify relevant reports?
- Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?
- Were restrictions based on date, publication format, or language appropriate?
- Were efforts made to minimise error in selection of studies?

Domain 3. Data collection and study appraisal
- Were efforts made to minimise errors in data collection?
- Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?
- Were all relevant study results collected for use in the synthesis?
- Was risk of bias (or methodological quality) formally assessed by appropriate criteria?
- Were efforts made to minimise error in risk of bias assessment?

Domain 4. Synthesis and findings
- Did the synthesis include all studies that it should?
- Were all predefined analyses reported or departures explained?
- Was the synthesis appropriate given the nature and similarity of research questions, study designs, and outcomes across included studies?
- Was between-study variation (heterogeneity) minimal or addressed in the synthesis?
- Were the findings robust (e.g. as demonstrated through funnel plot or sensitivity analyses)?
- Were biases in primary studies minimal or addressed in the synthesis?

We will rate each criterion as Y = Yes, PY = Probably yes, PN = Probably no, N = No, NI = No information.
We will then interpret each domain as having 'Low', 'High', or 'Unclear' concerns for bias.

Phase 3. Judging the risk of bias

Concerns from each domain are summarised.
We will then determine whether the conclusions are supported by the evidence presented.

- Did interpretation of the findings address all concerns identified in domains one through four?
- Was the relevance of identified studies to the review's research question appropriately considered?
- Did the review authors avoid emphasising results on the basis of their statistical significance?
- Risk of bias in the review? LOW/HIGH/UNCLEAR.

CONTRIBUTIONS OF AUTHORS

SC - drafting of background and protocol methods.

SRD - drafting of background and protocol methods.

CP - drafting of background and protocol methods.

AG - drafting of background and protocol methods.

FEB - drafting of background and protocol methods.

CL - drafting of protocol methods, critical review of background.

DECLARATIONS OF INTEREST

SC: none known.

SRD: none known.

CP: none known.

AG: none known.

FEB: none known.

CL: none known.

SOURCES OF SUPPORT

Internal sources

- Cardiff University, UK.

CP's time is paid for in part by Cardiff University.

- Monash University, Australia.

AG's salary is paid in part by Monash University.
CL's time is supported by an International Postgraduate Research Scholarship administered through Monash University.

- Auckland District Health Board, New Zealand.

SRD's salary is paid by Auckland District Health Board.

- Royal Children's Hospital Foundation, Melbourne, Australia.

FEB's time was funded in part by a grant from the Royal Children's Hospital Foundation, Melbourne, Australia.

- Murdoch Children's Research Institute, Australia.

FEB's time was funded in part by a Melbourne Children's Clinician Scientist Fellowship, administered by the Murdoch Children's Research Institute, Melbourne, Australia.

External sources

- National Health and Medical Research Council, Canberra, Australia, Australia.

FEB's time is funded in part by Practitioner Fellowship GNT1124466.

SRD, FEB, SC, and AG are members of the Paediatric Research in Emergency Departments International Collaborative (PREDICT) Network, which is funded by a Centre of Research Excellence grant (GNT1058560).

- Health Research Council of New Zealand, New Zealand.

SRD's time was funded in part by the Health Research Council of New Zealand (HRC13/556).

- Australian Government, Australia.

CL's time is funded in part by an Australian Postgraduate Award, administered through Monash University.

- Australasian College for Emergency Medicine Foundation, Australia.

SC's time is funded in part by the Al Spilman Early Career Researcher Grant from the ACEM Foundation.